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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,409	07/09/2003	Sharlene Adams	I0248.70024US00	9289

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,409	ADAMS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-17,139,142,144,166,251-260,338 and 340-348* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-17,139,142,144,166,251-260,338 and 340-348* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/16/2007 has been entered.

Claims 1-3, 7-17, 139, 142, 144, 166, 251-260, 338 and 340-348 are currently pending and under consideration.

The Declaration under 37 CFR 1.132 filed on 4/27/2007 by Margaret J. Uprichard is insufficient to overcome the rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Kaminski et al. (US 6,090365, 2000) as evidenced by Ajay et al. (Proc. Am. Soc. Clin. Oncol. 2001; 20: Abstr 1118) in view of Wallner et al. (WO 00/71135, 2000, IDS) and under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9) in view of Wallner et al. (WO 00/71135, 2000, IDS) as set forth in the previous Office action because: while the Declaration concludes that the ability of Formula I agents (i.e., Talabostat) to enhance the anti-cancer effect of an antibody such as an anti-CD20 antibody could not have been predicted and thus was unexpected prior to the invention, the Declaration does not appear to set forth whether the properties differ to such an extent that the difference is really unexpected. For example, Wallner et al. discloses that the efficacy of existing therapies useful for treating cancer such as monoclonal antibodies and/or localization radiation are improved when used in combination with an agent of Formula I such as Val-boroPro (page 22, lines 6-9, 27-28 and page 25, line 23). As such, one of skill in the art would reasonably expect that by using a combination of an agent of Formula I and an anti-CD20 antibody would result in an improved therapeutic efficacy, e.g., an enhancement of anti-cancer effects. Moreover, the Declaration describes the results of a Phase II clinical trial relating to the anti-tumor responses observed in human subjects received Talabostat (i.e., Val-boroPro, PT-100) and the anti-CD20 antibody rituximab, wherein the combination of talabostat and rituximab shows promising activity in patients with advanced CLL who have failed prior rituximab (see Declaration/Poster

conclusion). However, the clinical trials do not appear to set forth whether the addition of Talabostat increased the efficacy of rituximab because it is unclear whether Talabostat alone has tumor inhibiting activity in patients with advanced CLL who have failed prior rituximab

The Declaration under 37 CFR 1.132 filed on 4/27/2007 by Barry Jones, is insufficient to overcome the rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Kaminski et al. (US 6,090365, 2000) as evidenced by Ajay et al. (Proc. Am. Soc. Clin. Oncol. 2001; 20: Abstr 1118) in view of Wallner et al. (WO 00/71135, 2000, IDS) and under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9) in view of Wallner et al. (WO 00/71135, 2000, IDS) as set forth in the previous Office action because: while the Declaration concludes that the ability of Formula I agents (i.e., PT-100) to enhance the anti-cancer effect of an antibody such as an anti-CD20 antibody could not have been predicted and thus was unexpected prior to the invention, the Declaration does not appear to set forth whether the properties differ to such an extent that the difference is really unexpected. For example, Wallner et al. discloses that the efficacy of existing therapies useful for treating cancer such as monoclonal antibodies and/or localization radiation are improved when used in combination with an agent of Formula I such as Val-boroPro (page 22, lines 6-9, 27-28 and page 25, line 23). As such, one of skill in the art would reasonably expect that a combination of an agent of Formula I and an anti-CD20 antibody would result in an improved therapeutic efficacy, e.g., an enhancement of anti-cancer effects. Moreover, the Declaration describes the results of PT-100 and control IgG, anti-CD20 antibody rituximab alone and PT-100 and anti-CD20 antibody rituximab together on tumor volume. In particular, the Declaration teaches that treatment with PT-100 (Val-boroPro) and a normal human IgG or with rituximab alone resulted in significantly ($p<0.05$) tumor growth inhibition, wherein the combined treatment with PT-100 and rituximab inhibited tumor growth to a significantly ($p<0.05$) greater extent than did treatment with PT-100 and normal IgG or treatment with rituximab alone. However, one of ordinary skill in the art would not be able to reasonably conclude which agent had an enhancing effect on the other. In other words, one of ordinary skill in the art could reasonably conclude that rituximab enhanced the anti-cancer effects of PT-100 or, alternatively, PT-100 enhanced the anti-cancer effects of rituximab.

Information Disclosure Statement

The Information Disclosure Statement filed on July 20, 2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 8-17, 139, 144, 166, 251-260, 338 and 340-347 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaminski et al. (US 6,090365, 2000, *of record*) as evidenced by Ajay et al. (Proc. Am. Soc. Clin. Oncol. 2001; 20: Abstr 1118, *of record*) in view of Wallner et al. (WO 00/71135, 2000, IDS, *of record*).

Kaminski et al. teach a method of treating a lymphoma in a patient comprising administering a therapeutic dose of a radiolabelled anti-CD20 antibody, wherein the radiometric dose received by the patient is limited to a level that toxicity to bone marrow is not significant and reconstitution of hematopoietic function, by bone marrow transplantation or by other means, is not required (column

5, lines 45-53). With regards to the administration, the patent teaches that the anti-CD20 antibodies can be administered by intravenous injection or intralymphatic injection (column 10, lines 8-24). In addition to treating lymphoma's, the patent also teaches that the method can be applied to the treatment of a variety of leukemia's such as hairy cell leukemia and chronic myeloblastic leukemia's (column 6, lines 10-19). Moreover, the patent teaches that the method of treatment is amendable to the treatment of chronic diseases or diseases that have relapsed after a period of remission (column 6, lines 20-24). Thus, while Kaminski et al. does not specifically teach that the radiolabelled anti-CD20 antibody is tositumomab, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art disclosure because as evidenced by Ajay et al., tositumomab is available through Coulter Pharmaceuticals the assignee of the US 6,090,365 patent. Thus, the claimed antibody appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Kaminski et al. does not explicitly teach a method of enhancing treatment with an anti-CD20 antibody or a fragment thereof in a subject having cancer comprising administering an agent of Formula I and an anti-CD20 antibody or a fragment thereof.

Wallner et al teach (abstract) a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II as shown in the specification on page 25, wherein formula II is a cyclic derivative. With regards to the agent of Formula I, the WO document teaches that the agent comprises the formula PR, wherein P is a targeting group which binds to the reactive site of post praline-cleaving enzyme, and R is a reactive group capable of reacting with a functional group in a post proline cleaving enzyme (page 8, lines 12-14). Specifically, the reference teaches (page 2, line 25 to page 3, line 17) that the agent is Val-boro-Pro, wherein the agent may be a racemic mixture of the D/L isomers or may be the all L-isomer. Wallner et al. further teaches (page 43, lines 17+ and Figure 1) that IL-6 levels were increased upon the addition

of the agent to Fischer D+ rat and BM stromal cells. Moreover, Wallner et al. disclose (page 22, lines 6-9, 27-28 and page 25, line 23) that the method may further comprise administering the agent in combination with existing therapies for cancer such as the use of monoclonal antibodies and/or localization radiation, wherein the efficacy of the existing therapy is improved. With regards to the administration, the WO document teaches (page 22, lines 11-13 and page 27, lines 28-29) that the agents may be administered prior to, concurrent with, or following the existing therapy. Specifically, the WO document teaches (page 28, lines 24-27) that if the existing cancer is a monoclonal antibody, the treatment can performed at sub-lethal dose. The reference further teaches that the agent may be administered to those patients who may have been immunosuppressed (reduction in lymphoid cells) such as in a patient treated for lymphoma, provided that at the time the treatment the subject has protective or normal levels of hemopoeitic cells (page 20, lines 37-30). In addition to those patients suffering from cancer, Wallner et al. teach that the subject may be HIV negative (page 3, line 27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat cancer. In the instant case, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). As such, one of skill in the art would have been motivated to do so because Wallner et al. teach that the boroproline derivatives when used in combination with an existing therapy such as localization radiation (e.g., radioimmunotherapy of cancer) are useful in improving the efficacy of the existing therapies for treating conditions such as cancer. Thus, one of ordinary skill in the art would have reasonably expectation that by administering a compound of formula I or II in combination with the radiolabelled anti-CD20 antibody as taught by Kaminski et al., one would achieve a method of enhancing the efficacy of the radiolabelled anti-CD20 antibody.

Moreover, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the administration times and/or routes of administration of the antibody and the compound of Formula I. One would have been motivated to do so because the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results, see In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson,

39 F.2d 975. Thus, one would have a reasonable expectation that the administration of the antibody simultaneously, sequentially or prior to the administration of the second therapeutic agent would result in the treatment of a tumor.

In response to this rejection, Applicants assert that a prima facie case of obviousness has not been made because it was unpredictable prior to the invention that enhanced efficacy of an antibody (such as rituximab) could be achieved by combining it with an agent of Formula I (such as Val-boroPro). For example, Applicants assert that one reason for the lack of predictability is the difference in the mechanisms of action of these agents as understood prior to the invention, wherein the anti-cancer effect of antibodies such as anti-CD20 antibodies is mediated via an immunological mechanism of action, and prior to the invention, there was no belief that Formula I agents such as Val-boroPro could mediate effects via an immunological mechanism. Therefore, Applicants assert that the ability of a presumably non-immunological acting anti-cancer agent to enhance the efficacy of an immunologically acting anti-cancer antibody could not have been predicted and thus was unexpected. In addition, Applicants assert that the combination of references does not result in each and every limitation of the rejected claims which commonly recite that treatment with an anti-CD20 antibody is enhanced by an agent of Formula I. Moreover, Applicants assert that the Examiner has not met his burden with respect to the previously submitted Declarations under 37 CFR 1.132 Drs. Barry Jones and Margaret Upichard which described unexpected findings related to the combined use of an agent of Formula I and an anti-CD20 antibody. In particular, Applicants assert that as stated in the Jones Declaration, the effect of the combined use of an agent of Formula I with an anti-CD20 antibody was unexpected and unpredictable at least because the knowledge in the prior art to the invention taught different mechanisms of action of these agents. Regarding the Uprichard Declaration, Applicants assert that as stated in the Uprichard Declaration, the results demonstrate that the therapeutic effect of the anti-CD20 antibody can be enchanced by using the antibody in conjunction with a Formula I agent, and thus further support the invention as described in this application and as claimed. With respect to the Examiner's reliance on In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983), Applicants submit that nothing in the cited art teaches that the agent of Formula I enhances the effects of an anti-CD20 antibody or fragment thereof. Lastly, Applicants disagree with the Examiner's assertions regarding the administration regimens of the rejected claims because of the unexpected results discussed above, and further, that

some of the rejected claims recite particular administration regiments that go beyond mere orders of administration.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions with respect to the unpredictability of combining the two agents, the Examiner acknowledges that that the two agents, i.e., an anti-CD20 antibody and an agent of Formula I, have different mechanisms of action. However, the Examiner recognizes that the mere difference with respect to the agent's mechanism of action, in general, does not appear to negate their combination. For example, one of skill in the art would recognize that anti-CD20 antibodies, in particular rituximab, have been increasingly and successfully used in conjunction with chemotherapeutic agents which have varying mechanisms of action, see for example, Vose et al. (J. Clin. Onology 2001; 19: 389-397); Czuczman et al. (J. Clin. Oncology 1999; 17: 268-276); and Emmanouilides et al. (Cancer Biotherapy & Biopharmaceuticals 2002; 17: 621-630). Moreover, the Examiner recognizes that both anti-CD20 antibodies and agents of Formula I have been individually taught in the prior art to be effective at treating cancer. As such, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. In addition, with respect to Applicants arguments pertaining to the combination not teaching all of the limitations, the Examiner recognizes that the limitation of enhancing the treatment with an anti-CD20 antibody has not been given patentable weight because the limitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Assuming, *arguendo*, that the limitation is given patentable weight or Applicants amend the claims to incorporate this limitation within the "body" of the claims, the Examiner recognizes that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve

the same advantage or result discovered by applicant. >See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). (Emphasis added). In the instant case, the motivation to combine the teachings of the references lies in both being individually taught in the prior art to be effective at treating cancer; and further, Wallner et al. teachings that the boroproline derivatives when used in combination with an existing therapy such as localization radiation (e.g., radioimmunotherapy of cancer) are useful in improving the efficacy of the existing therapies for treating conditions such as cancer. With respect to the Declaration's filed in response to the previous Office Action, the Examiner has considered the Declarations as they relate to the instant rejections and has not found them persuasive for the reasons set forth above, which have been incorporated herein. Regarding Applicants arguments pertaining to the Examiner's reliance on In re Sernaker, the Examiner recognizes that the limitation of enhancing the treatment with an anti-CD20 antibody has not been given patentable weight because the limitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Regarding Applicants assertions with respect to the administration regimens, the Examiner acknowledges that Applicants note the unexpected results discussed above. However, the Examiner recognizes that it does not appear the asserted "unexpected" results are a direct result of the different administration regimens. As such, these arguments are moot.

Claims 1-3, 7-17, 139, 144, 251-260, 338 and 348 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998, *of record*) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9, *of record*) in view of Wallner et al. (WO 00/71135, 2000, IDS, *of record).*

Anderson et al. teach a method of treating lymphoma comprising administering an immunologically active anti-CD20 antibody, radiolabeled anti-CD20 antibody or a combination of an anti-CD20 antibody and radiolabeled anti-CD20 antibody (abstract). With regards to the administration of the anti-CD20 antibody, the patent teaches that the anti-CD20 antibodies and

radiolabeled antibodies are administered by intravenous, intramuscular, subcutaneous or intraperitoneal routes (column 7, lines 55-61). Moreover, the patent teaches that depletion levels of peripheral blood B lymphocytes was maintained for up to 7 days; after this period, B cell recovery began (column 25, lines 59-64). Thus, while Anderson et al. does not specifically teach that the anti-CD20 antibody is rituximab, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art disclosure because as evidenced by Grillo-Lopez et al, rituximab is clinically developed by IDEC Pharmaceutical Corporation which is the assignee of the US 5,776,456 patent. Thus, the claimed antibody appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Anderson et al. does not explicitly teach a method of enhancing treatment with an anti-CD20 antibody or a fragment thereof in a subject having cancer comprising administering an agent of Formula I and an anti-CD20 antibody or a fragment thereof.

Wallner et al teach (abstract) a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II as shown in the specification on page 25, wherein formula II is a cyclic derivative. With regards to the agent of Formula I, the WO document teaches that the agent comprises the formula PR, wherein P is a targeting group which binds to the reactive site of post praline-cleaving enzyme, and R is a reactive group capable of reacting with a functional group in a post proline cleaving enzyme (page 8, lines 12-14). Specifically, the reference teaches (page 2, line 25 to page 3, line 17) that the agent is Val-boro-Pro, wherein the agent may be a racemic mixture of the D/L isomers or may be the all L-isomer. Wallner et al. further teaches (page 43, lines 17+ and Figure 1) that IL-6 levels were increased upon the addition of the agent to Fischer D+ rat and BM stromal cells. Moreover, Wallner et al. disclose (page 22, lines 6-9, 27-28 and page 25, line 23) that the method may further comprise administering the agent in combination with existing therapies for cancer such as the use of monoclonal antibodies and/or

localization radiation, wherein the efficacy of the existing therapy is improved. With regards to the administration, the WO document teaches (page 22, lines 11-13 and page 27, lines 28-29) that the agents may be administered prior to, concurrent with, or following the existing therapy. Specifically, the WO document teaches (page 28, lines 24-27) that if the existing cancer is a monoclonal antibody, the treatment can be performed at sub-lethal dose. The reference further teaches that the agent may be administered to those patients who may have been immunosuppressed (reduction in lymphoid cells) such as in a patient treated for lymphoma, provided that at the time the treatment the subject has protective or normal levels of hemopoeitic cells (page 20, lines 37-30). In addition to those patients suffering from cancer, Wallner et al. teach that the subject may be HIV negative (page 3, line 27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat cancer. In the instant case, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). As such, one of skill in the art would have been motivated to combine the references because Wallner et al. teach that the boroproline derivatives when used in combination with an existing therapy such as localization radiation (e.g., radioimmunotherapy of cancer) are useful for improving the efficacy of the existing therapies for treating conditions such as cancer. Thus, one of ordinary skill in the art would have reasonably expectation that by administering a compound of formula I or II in combination with the an antiCD20 antibody or radiolabelled anti-CD20 antibody as taught by Anderson et al., one would achieve a method of enhancing the efficacy of the existing anti-CD20 therapy.

Moreover, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the administration times and/or routes of administration of the antibody and the compound of Formula I. One would have been motivated to do so because as taught by Wallner et al. the boroproline derivatives can be used for the treatment of patients who may been myelosuppressed or immunosuppressed, provided that at the time of treatment the subject has protective levels of hemopoeitic cells, whereas Anderson et al. teach that normal levels

of lymphatic cells after 7 days post anti-CD20 infusion. As such, the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results, see In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson, 39 F.2d 975. Thus, one would have a reasonable expectation that the administration of the antibody prior to or after the administration of the second therapeutic agent would result in the treatment of B-cell lymphoma.

In response to this rejection, Applicants assert that a prima facie case of obviousness has not been made because it was unpredictable prior to the invention that enhanced efficacy of an antibody (such as rituximab) could be achieved by combining it with an agent of Formula I (such as Val-boroPro). For example, Applicants assert that one reason for the lack of predictability is the difference in the mechanisms of action of these agents as understood prior to the invention, wherein the anti-cancer effect of antibodies such as anti-CD20 antibodies is mediated via an immunological mechanism of action, and prior to the invention, there was no belief that Formula I agents such as Val-boroPro could mediate effects via an immunological mechanism. Therefore, Applicants assert that the ability of a presumably non-immunological acting anti-cancer agent to enhance the efficacy of an immunologically acting anti-cancer antibody could not have been predicted and thus was unexpected. In addition, Applicants assert that the combination of references does not result in each and every limitation of the rejected claims which commonly recite that treatment with an anti-CD20 antibody is enhanced by an agent of Formula I. Moreover, Applicants assert that the Examiner has not met his burden with respect to the previously submitted Declarations under 37 CFR 1.132 Drs. Barry Jones and Margaret Upichard which described unexpected findings related to the combined use of an agent of Formula I and an anti-CD20 antibody. In particular, Applicants assert that as stated in the Jones Declaration, the effect of the combined use of an agent of Formula I with an anti-CD20 antibody was unexpected and unpredictable at least because the knowledge in the prior art to the invention taught different mechanisms of action of these agents. Regarding the Uprichard Declaration, Applicants assert that as stated in the Uprichard Declaration, the results demonstrate that the therapeutic effect of the anti-CD20 antibody can be enchanced by using the antibody in conjunction with a Formula I agent, and thus further support the invention as described in this application and as claimed. With respect to the Examiner's reliance on In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983), Applicants submit that nothing in the cited art teaches that the agent of Formula I enhances the effects of an anti-CD20 antibody or fragment

thereof. Lastly, Applicants disagree with the Examiner's assertions regarding the administration regimens of the rejected claims because of the unexpected results discussed above, and further, that some of the rejected claims recite particular administration regiments that go beyond mere orders of administration.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions with respect to the unpredictability of combining the two agents, the Examiner acknowledges that that the two agents, i.e., an anti-CD20 antibody and an agent of Formula I, have different mechanisms of action. However, the Examiner recognizes that the mere difference with respect to the agent's mechanism of action, in general, does not appear to negate their combination. For example, one of skill in the art would recognize that anti-CD20 antibodies, in particular rituximab, have been increasingly and successfully used in conjunction with chemotherapeutic agents which have varying mechanisms of action, see for example, Vose et al. (J. Clin. Onology 2001; 19: 389-397); Czuczman et al. (J. Clin. Oncology 1999; 17: 268-276); and Emmanouilides et al. (Cancer Biotherapy & Biopharmaceuticals 2002; 17: 621-630). Moreover, the Examiner recognizes that both anti-CD20 antibodies and agents of Formula I have been individually taught in the prior art to be effective at treating cancer. As such, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. In addition, with respect to Applicants arguments pertaining to the combination not teaching all of the limitations, the Examiner recognizes that the limitation of enhancing the treatment with an anti-CD20 antibody has not been given patentable weight because the limitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Assuming, *arguendo*, that the limitation is given patentable weight or Applicants amend the claims to incorporate this limitation within the "body" of the claims, the Examiner recognizes that the reason or motivation to

modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. >See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). (Emphasis added). In the instant case, the motivation to combine the teachings of the references lies in both being individually taught in the prior art to be effective at treating cancer; and further, Wallner et al. teachings that the boroproline derivatives when used in combination with an existing therapy such as localization radiation (e.g., radioimmunotherapy of cancer) are useful in improving the efficacy of the existing therapies for treating conditions such as cancer. With respect to the Declaration's filed in response to the previous Office Action, the Examiner has considered the Declarations as they relate to the instant rejections and has not found them persuasive for the reasons set forth above, which have been incorporated herein. Regarding Applicants arguments pertaining to the Examiner's reliance on In re Sernaker, the Examiner recognizes that the limitation of enhancing the treatment with an anti-CD20 antibody has not been given patentable weight because the limitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Regarding Applicants assertions with respect to the administration regimens, the Examiner acknowledges that Applicants note the unexpected results discussed above. However, the Examiner recognizes that it does not appear the asserted "unexpected" results are a direct result of the different administration regimens. As such, these arguments have not been found persuasive.

Claims 340-347 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998, *of record*) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9, *of record*) in view of Wallner et al. (WO 00/71135, 2000, IDS, *of record*) in further view of Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9, *of record*).

Anderson et al. in view of Wallner et al. teach, as applied to claims 1-3, 7-17, 139, 144, 251-260, 338 and 348), a method of treating B-cell lymphoma comprising administering an

immunologically effective amount of an anti-CD20 antibody in combination with a boroproline derivative.

The combination of Anderson et al. in view of Wallner et al. does not explicitly teach that the b-cell lymphoma is Non-Hodgkin's lymphoma or a refractory form of Non-Hodgkin's lymphoma.

Grillo-Lopez et al. disclose that rituximab has been approved by the FDA for the treatment of relapsed or refractory, CD20 positive, B-cell, low-grade or follicular non-Hodgkin's lymphoma.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat Non-Hodgkin's lymphoma or refractory non-Hodgkin's lymphoma. One would have been motivated to do so because as taught by Grillo-Lopez et al., rituximab has already been taught in the prior art and approved by the FDA for the treatment of non-Hodgkin's lymphoma and refractory non-Hodgkin's lymphoma. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient suffering from non-Hodgkin's lymphoma or refractory non-Hodgkin's lymphoma the combination as taught by Anderson et al and Wallner et al., one would achieve method of enhancing the efficacy of the existing anti-CD20 therapy for non-Hodgkin's lymphoma or refractory non-Hodgkin's lymphoma.

In response to this rejection, Applicants assert that the combination of Anderson et al. Grillo-Lopez et al. and Wallner et al. does not render obvious claim 1 because no prima facie case of obviousness has been made as stated above or alternatively because of the secondary considerations of unexpected results as asserted in the previously submitted Declarations. Additionally, Applicants assert that the combination or the references does not render obvious the administration regimen of claim 343 because claim 343 requires administration of the agent of Formula I within 7 days of administration of the anti-CD20 antibody, whereas Anderson et al. teaches that normal levels of lymphatic cells are achieved 7 days after an anti-CD20 infusion. Thus, Applicants assert that the combination of references actually teaches away from the subject matter of claim 343.

These arguments have been carefully considered, but are not found persuasive.

Applicant's arguments pertaining to the combination of Anderson et al., Grillo-Lopez et al. and Wallner et al. have been addressed by the Examiner above and are herein incorporated. Regarding Applicants assertions that the combination teaches away from the claimed invention, the

Examiner recognizes that Applicants have not provided any arguments as to how the combination teaches away from the claimed invention. In the instant case, Applicant should submit an argument pointing out disagreements with the examiner's contentions. Applicant must also discuss the references applied against the claims, explaining how the claims avoid the references or distinguish from them.

Claim 142 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kaminski et al. (US 6,090365, 2000, *of record*) as evidenced by Ajay et al. (Proc. Am. Soc. Clin. Oncol. 2001; 20: Abstr 1118, *of record*) in view of Wallner et al. (WO 00/71135, 2000, IDS, *of record*) and in further view of Buske et al. (European Journal of Cancer 1999; 35: 549-557, *of record*).

Kaminski et al in view of Wallner et al. teach, as applied to claims 1-3, 8-17, 139, 144, 166, 251-260, 338 and 340-347 above, a method of enhancing treatment with an anti-CD20 antibody or a fragment thereof in a subject having a lymphoma comprising administering a radiolabelled anti-CD20 antibody in combination with a therapeutically effective amount of a boroproline derivative. In addition to the treatment of lymphoma with a radiolabelled CD20 antibody alone, Kaminski et al. teach the treatment of lymphoma using a combination of anti-CD20 antibodies and radiolabelled antibodies (column 5, lines 54-60).

The combination of Kaminski et al. in view of Wallner et al. do not explicitly teach that an anti-CD20 antibody conjugated to a toxin.

Buske et al. disclose the emerging concepts monoclonal antibody therapy for B-cell non-Hodgkin's lymphomas. Specifically, the reference teaches that the cytolytic activity of the native Mab can be enhanced by coupling an antibody with a plant or bacterial toxin (page 551, 1st column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate a bacterial toxin or plant toxin to the anti-CD20 antibody as taught by Kaminski et al. in view of the teachings of Buske et al. One would have been motivated to do so because as taught by Buske et al., conjugation of a plant or bacterial toxin enhances the cytolyitic activity of the Mab. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by conjugating a plant or bacterial toxin to an anti-CD20 antibody, one would achieve a

method of enhancing the therapeutic effect of the anti-CD20 antibody on B-cell mediated non-Hodgkin's lymphoma.

In response to this rejection, Applicants assert that the combination of Kaminski et al. Gopal et al. and Wallner et al. does not render obvious claim 1 because no prima facie case of obviousness has been made as state above, or alternatively of the secondary consideration of unexpected results asserted in the previously submitted Declarations. Moreover, Applicants assert that the addition of Buske et al. does not cure the deficiencies of the prior combination of references nor does it negate the secondary consideration of unexpected results.

These arguments have been carefully considered, but are not found persuasive.

Applicant's arguments pertaining to the combination have been addressed by the Examiner above and are herein incorporated. Regarding Applicants assertions that Buske et al. does not cure the deficiencies of the prior combination of references, the Examiner recognizes that Applicants have not provided any arguments as to how Buske et al. does not cure these deficiencies of the prior combination of references. In the instant case, Applicant should submit an argument pointing out disagreements with the examiner's contentions. Applicant must also discuss the references applied against the claims, explaining how the claims avoid the references or distinguish from them.

Claim 142 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998, *of record*) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9, *of record*) in view of Wallner et al. (WO 00/71135, 2000, IDS, *of record*) and in further view of Buske et al. (European Journal of Cancer 1999; 35: 549-557, *of record*).

Anderson et al. in view of Wallner et al. teach, as applied to claims 1-3, 7-17, 139, 144, 251-260, 338 and 348), a method of treating B-cell lymphoma comprising administering an immunologically effective amount of an anti-CD20 antibody in combination with a boroproline derivative. Specifically, Anderson et al. teach a method of treating lymphoma comprising administering an immunologically active anti-CD20 antibody, radiolabeled anti-CD20 antibody or a combination of an anti-CD20 antibody and radiolabeled anti-CD20 antibody (abstract).

The combination of Anderson et al. in view of Wallner et al. does not explicitly teach that the anti-CD20 antibody is conjugated to a toxin such as a plant or bacterial toxin.

Buske et al. disclose the emerging concepts monoclonal antibody therapy for B-cell non-Hodgkin's lymphomas. Specifically, the reference teaches that the cytolytic activity of the native Mab can be enhanced by coupling an antibody with a plant or bacterial toxin (page 551, 1st column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate a bacterial toxin or plant toxin to the anti-CD20 antibody as taught by Anderson. in view of the teachings of Buske et al. One would have been motivated to do so because as taught by Buske et al., conjugation of a plant or bacterial toxin enhances the cytolyitic activity of the Mab. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by conjugating a plant or bacterial toxin to an anti-CD20 antibody, one would achieve a method of enhancing the therapeutic effect of the anti-CD20 antibody on B-cell mediated non-Hodgkin's lymphoma.

In response to this rejection, Applicants assert that the combination of Anderson et al., Grillo-Lopez et al. and Wallner et al does not render obvious claim 1 because no prima facie case of obviousness has been made as state above, or alternatively of the secondary consideration of unexpected results asserted in the previously submitted Declarations. Moreover, Applicants assert that the addition of Buske et al. does not cure the deficiencies of the prior combination of references nor does it negate the secondary consideration of unexpected results.

These arguments have been carefully considered, but are not found persuasive.

Applicant's arguments pertaining to the combination have been addressed by the Examiner above and are herein incorporated. Regarding Applicants assertions that Buske et al. does not cure the deficiencies of the prior combination of references, the Examiner recognizes that Applicants have not provided any arguments as to how Buske et al. does not cure these deficiencies of the prior combination of references. In the instant case, Applicant should submit an argument pointing out disagreements with the examiner's contentions. Applicant must also discuss the references applied against the claims, explaining how the claims avoid the references or distinguish from them.

Therefore, NO claim is allowed

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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